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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,435	11/26/2003	Weihong Xiong	01121-17272	6215

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M. Wayne Western
THORPE NORTH & WESTERN, LLP
P.O. Box 1219
Sandy, UT 84091-1219

EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,435	XIONG ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2008* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-84,86-97,102 and 103* is/are pending in the application.

4a) Of the above claim(s) *53-80 and 87-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-84,86,102 and 103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *02/29/08* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The receipt is acknowledged of applicants' amendment and request for RCE, both filed 02/15/2008; and IDS filed 02/28/2008.

Claims 1-52, 85, 98-101 have been canceled.

Claims 53-84, 86-97, 102-103 are pending.

Claims 53-80, 87-97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Groups I, and II, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/21/2007.

Claims 81-84, 86, 102, and 103 are included in the prosecution.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 81-84, 86, 102, and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,352,715 ('715) with the effective filing date February 19, 1998 in view of US 6,365,178 ('178) with the effective filing date September 08, 1998.

US '715 teaches a transdermal drug delivery system to administer huperzine A in a controlled release skin patch designed for once-a-week application to treat Alzheimer disease (AD) (abstract; col.3, lines 55-65; col.4, lines 7-15; col.9, lines 1-7, 31). The patch comprises polyacrylate adhesive layer containing huperzine (col.9, lines 32-35; col.14, lines 65-67). The reference suggests the use of co-solvents to increase skin permeability of huperzine A (col.8, lines 65-67).

However, US '715 does not teach the blood plasma levels of huperzine provided by the transdermal system as instantly claimed.

The blood plasma levels are controlled by the amount of the drug included in the system as well as by the ingredients of the transdermal formulation used to deliver the huperzine such as the type of the adhesive, the permeation enhancers and other additives in the formulation.

Therefore, the claimed blood plasma levels of huperzine can be determined by one having ordinary skill in the art by manipulating the transdermal formulation containing the huperzine and the structure of the transdermal device delivering it. Additionally, individual patient-need is also a controlling factor in determination of the dose of huperzine.

It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller,* 105 USPQ 233.

US '175 does not explicitly teach the transdermal device comprises adhesive matrix and specific permeation enhancer as instantly claimed by claim 81.

US '178 teaches transdermal delivery device having adhesive matrix wherein the physical stability of the drug in the matrix is excellent and crystallization of the drug is inhibited (abstract). The adhesive matrix is suitable to deliver antiparkinsonism drugs and anticholinergic drugs (col.6, lines 18-20). The adhesive matrix comprises acrylic or rubber adhesives and permeation enhancer including fatty acid esters including lauryl lactate (col.6, line 42; col.7, lines 45-65; col.22, lines 36-38).

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a transdermal drug delivery system to deliver huperzine

to treat patients suffering from AD wherein the system comprises polyacrylate adhesive and may contain permeation enhancer as disclosed by US '715, and provide huperzine in adhesive matrix comprising permeation enhancer including fatty acid ester of lactic acid as disclosed by US '178 because US '715 disclosed huperzine as being capable to be provided combined with acrylic materials and enhancers and because US '178 teaches polyacrylate adhesive matrix comprising enhancers is suitable to deliver antiparkinsonism and anticholinergic drugs while such adhesive matrix shows excellent physical stability of the included drugs and inhibition of their crystallization, with reasonable expectation of having a transdermal delivery system to treat AD comprising huperzine in adhesive matrix comprising acrylate or rubber adhesive and fatty acid ester permeation enhancer wherein the matrix has excellent physical stability of the drug in the matrix without drug crystallization to provide the desired blood plasma levels of huperzine for extended time to treat the AD patients with great success.

4. Claims 81-84, 86, 102-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over CN 1111987 ('987) in view of US '178 and the article "Dermal Absorption Models in Toxicology and Pharmacology", provided by applicants.

CN '987 teaches a plaster for treating senile dementia with long activity life of 3-4 days comprising huperzine (abstract). CN '987 teaches the plaster containing adhesive layer containing 0.1 to 8% w/w of huperzine, and applicants used in all their examples 0.01 to 20% w/w of huperzine. Therefore, it is expected that the same amount of huperzine disclosed by the prior art to provide the same blood plasma level of huperzine

if it is present in the same formulation. The reference teaches combination of permeation enhancers including azone and fatty acid esters including ester of lauric acid (page 6; examples). The adhesive comprises polyacrylate (example1).

CN '987 does not teach explicitly teach the blood plasma levels of huperzine provided by the transdermal system as instantly claimed, however, it is expected that the plaster disclosed by CN '987 to provide the same blood plasma level of huperzine because it contains the same amount of the huperzine. The plasma levels are controlled by the amount of huperzine included in the system as well as by the ingredients of the transdermal formulation used to deliver the huperzine such as the type of the adhesive, the permeation enhancers and other additives in the formulation.

US '178 teaches transdermal delivery device having adhesive matrix wherein the physical stability of the drug in the matrix is excellent and crystallization of the drug is inhibited (abstract). The adhesive matrix is suitable to deliver antiparkinsonism drugs and anticholinergic drugs (col.6, lines 18-20). The adhesive matrix comprises acrylic or rubber adhesives and permeation enhancer including fatty acid esters including lauryl lactate (col.6, line 42; col.7, lines 45-65; col.22, lines 36-38).

Therefore, the art recognized the fatty acids esters as a penetration enhancer for drugs included in adhesive matrix.

CN '987 recognized fatty acid esters as permeation enhancer for huperzine, however, provided them combined with azone. It has been held that omission of an element and its function is obvious if the function of the element is not desired. *Ex parte Wu*, 10 USPQ 2031 (Bd. Pat. App. & Inter. 1989). See also *In re Larson*, 340 F.2d 965,

144 USPQ 347 (CCPA 1965); and *In re Kuhle*, 526 F.2d 553, 188 USPQ 7 (CCPA 1975).

The article "Dermal Absorption Models in Toxicology and Pharmacology" teaches that azone is effective as permeation enhancer in low concentration, however, the article stated that: "There have been several studies looking into the toxicity potential of azone and its analogues. Contradicting reports were published, some reporting that azone is moderate irritant,..... and others reporting that it is not irritating..... The skin irritation caused by azone may be the prim reason for not using it as a penetration enhancer in transdermal system."

This teaching may have motivated one having ordinary skill in the art at the time of the invention to exclude azone from the enhancer combination disclosed by CN '987 and get satisfied only by fatty acid esters because fatty acid esters were known at the time of the invention to be used as the sole enhancers in transdermal adhesive matrices as disclosed by US '178.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a transdermal drug delivery system to deliver huperzine to treat patients suffering from AD wherein the system comprises polyacrylate adhesive and permeation enhancer comprising azone and fatty acid esters as disclosed by CN '987, and eliminate azone from the matrix and maintain the fatty acid esters because the article "Dermal Absorption Models in Toxicology and Pharmacology" teaches the possibility of skin irritation caused by azone and because US '178 teaches adhesive matrix comprising fatty acid ester enhancer as sole enhancer and such matrix is

suitable to deliver antiparkinsonism and anticholinergic drugs and shows excellent physical stability of the drugs in the matrix and inhibition of their crystallization, with reasonable expectation of having a transdermal delivery system to treat AD comprising huperzine in polymer adhesive matrix comprising adhesive polymer and fatty acid ester permeation enhancer wherein the matrix has excellent physical stability of the drug in the matrix without drug crystallization to provide the desired blood plasma levels of huperzine for extended time to treat the AD patients with great success.

Response to Arguments

5. Applicant's arguments with respect to claims 81-84, 86, 102 and103 have been considered but are moot in view of the new ground(s) of rejection.

Applicants argue that US '715 teaches adjusting pH to enhance the delivery of huperzine, and co-solvents are suggested as possibly improving the penetration of neutral forms of huperzine, and CN '987 teaches azone that cause skin irritation and excluded by the present claims.

In response to these arguments, it is argued that a conclusion of obviousness under 35 U.S.C. 103 (a) does not require absolute predictability, only a reasonable expectation of success; and references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosure. *In re Bozek*, 163 USPQ 545 (CCPA 1969). US '715 and CN '987 suggested permeation enhancers, and according to the current rejection US '178 recognized fatty acid esters to enhance the delivery of cholinergic and antiparkinsonism drugs into the skin, and this teaching of US '178 would

have motivated one having ordinary skill in the art to include fatty acid esters into the transdermal delivery system disclosed by US '715 or CN '987.

Regarding the argument that CN '987 teaches azone that is excluded from the present claims, it has be held that omission of an element and its function is obvious if the function of the element is not desired. *Ex parte Wu*, 10 USPQ 2031 (Bd. Pat. App. & Inter. 1989). See also *In re Larson*, 340 F.2d 965, 144 USPQ 347 (CCPA 1965); and *In re Kuhle*, 526 F.2d 553, 188 USPQ 7 (CCPA 1975). It is applicants' choice not to use azone and excluding it from the system disclosed by CN '987. In any event, toxicity of azone and its skin irritation are not certain as taught by the article "Dermal Absorption Models in Toxicology and Pharmacology", provided by applicants. The article stated that: "There have been several studies looking into the toxicity potential of azone and its analogues. Contradicting reports were published, some reporting that azone is moderate irritant,..... and others reporting that it is not irritating..... The skin irritation caused by azone may be the prim reason for not using it as a penetration enhancer in transdermal system." Additionally, azone is disclosed as safe permeation enhancer for drugs and non-irritant to the skin by the article by Niazy "Differences in penetration-enhancing effect of Azone through excised rabbit, rat, hairless mouse, guinea pig and human skins", provided.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-

0595. The examiner can normally be reached on Monday-Thursday, 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Isis A Ghali/
Primary Examiner, Art Unit 1611

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